REMARKS

Status of the Claims

Claims 1, 11, 48, 65 and 74 have been amended. Specifically, claims 1 and 48 have been amended to recite that the peripheral artery disease is treated. Support for this amendment can be found throughout the specification, for example, on page 1, lines 9-11, and page 29, lines 18-22. Claim 48 has also been amended to recite that the therapeutically effective amount of FGF-2 is divided into two doses and a single dose is administered by intra-arterial, subcutaneous or intramuscular injection into each leg of the patient within a one hour period. Support for this amendment can be found in the original claims and throughout the specification, for example, on page 9, lines 17-21, and page 10, lines 15-18. Claim 65 has been amended to recite that the peak walking time is improved. Support for this amendment can be found throughout the specification, for example, on page 29, lines 18-22. Claim 74 has been amended to recite that the ankle-brachial index isimproved. Support for this amendment can be found throughout the specification, for example, on page 29, lines 18-22. Claim 11 has been amended to remove reference to the Figures in which the sequences corresponding to SEQ ID NO:2, 4, 6, and 8 are presented. No new matter is added by way of these amendments.

Claims 1-82 are now pending in the application. The Examiner's remarks in the Office Action are addressed below in the order set forth therein.

Clarification of the Claim for Priority

Applicant respectfully notes that U.S. Provisional Application No. 60/213,504 does provide support for claims drawn to the 146-residue human FGF-2 molecule set forth in SEQ ID NO:4 of the present utility application, and also provides support for co-administration of heparin or other glucosaminoglycan. See this provisional application at page 13, lines 1-10, for disclosure relating to SEQ ID NO:4 of the present application, and at page 12, lines 3-8, for disclosure relating to co-administration of heparin or other glucosaminoglycan. In view of this, Applicant respectfully submits that the claim for priority under 35 U.S.C. §119(e) be granted to U.S. Provisional Application No. 60/213,504, which has a filing date of June 22, 2000.

The Objection to the Specification Should Be Withdrawn

The Office Action has objected to the specification under MPEP §608.01 for containing embedded hyperlinks and/or other forms of browser-executable code. In response, Applicant notes that MPEP §608.01 specifically defines a hyperlink or a browser-executable code as "a URL placed between these symbols '< >' and 'http://' followed by a URL address." From this language it is clear that it is not a URL which is itself objectionable, only the hyperlink that results from the enclosure of a URL within the "< >" pair or after the "http://" character string, an interpretation which is consistent with the policy goal of preventing live web links in documents on the USPTO web page that might direct a user to a commercial site over which the USPTO has no control, rather than any policy against URLs *per se*. See MPEP §608.01.

The URLs contained in the specification are not live weblinks such as hyperlinks or browser-executable code. This can be seen definitively when viewing the published application on the USPTO website, where there are no live weblinks present. Because these URLs are not hyperlinks or browser-executable code as defined in MPEP §608.01, the objection should be withdrawn.

The Objection to the Claims Should Be Withheld Pending Resolution of Allowability of Generic and Subgeneric Claims

Claims 1-82 are objected to because the claims read on non-elected subject matter. Applicant respectfully notes that in responding to the restriction requirement, Applicant elected FGF-2 as the species of FGF and heparin as the species of proteoglycan for prosecution on the merits to which the claims would be restricted in the event that no generic (those drawn to any FGF) or subgeneric (those drawn to heparin or other proteoglycan) claim be held to be allowable. With such an election, Applicant is entitled to further consideration of additional species in the event a generic claim is held to be allowable. 37 C.F.R. §1.141(a). In view of this, Applicant elects to withhold amendments to the generic and subgeneric claims of this application until the issue regarding allowability of the generic and subgeneric claims has been resolved.

The Rejection of Claim 11 Under 35 U.S.C. § 112, Second Paragraph, Should Be Withdrawn

Claim 11 has been rejected as indefinite for failing to particularly point out and distinctly claim the subject matter that Applicant regards as the invention. Claim 11 has been amended to remove reference to the figures, thereby obviating the Examiner's concern. Therefore, Applicant respectfully requests that this rejection be withdrawn.

The Nonstatutory Double-Patenting Rejection Should Be Withdrawn

The Examiner has rejected claims 1-82 under the judicially created doctrine of obvious-type double patenting over claims 1-58 of U.S. Patent No. 6,440,934 (hereinafter "the '934 patent) in view of Moyer *et al.* (1998) *Exp. Opin. Ther. Patents* 8(110):1425-1446 (hereinafter "Moyer *et al.*). This rejection is respectfully traversed.

The present invention is directed to a method for treating peripheral artery disease (PAD) in a patient, comprising administering a therapeutically effective amount of fibroblast growth factor (FGF) that is divided into two doses and a single dose is administered into each leg of the patient within a one hour period, whereby said peripheral artery disease is treated. This administration protocol also finds use in improving peak walking time in a patient with intermittent claudication (claims 65-73), and in improving ankle-brachial index in a patient with intermittent claudication (claims 74-82).

The '934 patent claims a method for treating a human patient for coronary artery disease (CAD), comprising administering a therapeutically effective amount of a recombinant FGF-2 into one or more coronary vessels or into a peripheral vein. Moyer *et al.* discuss several animal models demonstrating the beneficial effects of FGF-2 on stimulating angiogenesis. These models include a rat model of peripheral artery insufficiency, a rabbit model of severe leg ischemia, and rat and rabbit models of severe unilateral hind limb ischemia. The Examiner has stated that claims 1-82 of the present application are not patentably distinct from claims 1-58 of U.S. Patent No. 6,440,934 in view of Moyer *et al.* Applicant respectfully disagrees with the Examiner's position for the following reasons.

In assessing obviousness-type double patenting, the analysis parallels the guidelines for a 35 U.S.C. §103(a) rejection, with the exception that the patent serving as the basis for the

double-patenting rejection is not considered prior art. MPEP 804.II.B.1, citing to *In re Braithwaite*, 379 F.2d 594, 154 USPQ 29 (CCPA 1967). Therefore, the Examiner has the burden of establishing a *prima facie* case of obviousness.

To establish a *prima facie* case of obviousness (1) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or combine the reference teachings; (2) there must be a reasonable expectation of success; and (3) the prior art reference(s) must teach or suggest all the claim limitations. MPEP §2143. Applicant respectfully submits that when establishing a *prima facie* case of obviousness, one must consider the teachings of the cited reference(s) as a whole, including portions that would lead away from the claimed invention. MPEP §2141.02. It is Applicant's contention that a *prima facie* case of obviousness has not been established in the present application as the motivation to modify either one of these references, or to combine the teachings of these two cited references, to arrive at Applicant's claimed invention is lacking. Even if such motivation were to exist, these references do not provide to one of skill in the art a reasonable expectation of success. Further, these references fail to teach or suggest all of the limitations set forth in the pending claims.

Applicant submits that claims 1-82 of the present invention are patentably distinct from claims 1-58 of the '934 patent. As an initial matter, PAD and CAD are separate and distinct clinical conditions, with discrete symptoms and treatments. The successful treatment of one does not provide a reasonable expectation of success for treating the other, particularly when different treatment regimens are being used. Furthermore, claims 1-58 of the '934 patent do not meet all the limitations of claims 1-82 of the present application. Amended claims 1-82 include the claim limitation that peripheral artery disease is treated or that a specific clinical endpoint (i.e., improved peak walking time or improved ankle-brachial index) is achieved. Treatment of PAD and improvement in these specific clinical endpoints would not necessarily result by practicing any of the methods claimed in the '934 patent. Furthermore, the '934 patent does not teach nor does it require that the therapeutically effective amount of FGF be divided into two doses and that a single dose be administered into each leg of the patient within a one hour period. Accordingly, Applicant submits that these inventions are patentably distinct.

With respect to the Examiner's comment that claims to treatment of CAD read on claim to treatment of PAD, the amended claims of the present invention require as a claim limitation the treatment of PAD or an improved peak walking time or improved ankle-brachial index in a patient with intermittent claudication. Such clinical results are not necessarily obtained using the methods of the '934 patent. As mentioned above, there is no reasonable expectation of success in treating PAD or in improving peak walking time or ankle-brachial index of a patient with intermittent claudication by using the methods claimed in the '934 patent. Furthermore, the '934 patent when combined with the teachings of the Moyer *et al.* reference fails to teach all the claim limitations. Moyer *et al.* does not provide guidance for dividing the therapeutically effective dose of FGF as taught by the claims of the '934 patent into two doses, with a single one of these doses being administered into each leg of a PAD patient within a one hour period, and this guidance is not provided by the '934 patent. As all the claim limitations are not met by the combined teachings of these two cited references, a *prima facie* case of obviousness has not been met.

Regarding the Examiner's objection to the use of basic FGF or SEQ ID NO:2 in the methods of the presently claimed invention, Applicant acknowledges that this sequence is the same sequence disclosed in the '934 patent. However, for the reasons noted above, the methods of the present invention are patentably distinct from those recited in claims 1-53 of the '934 patent and are not rendered obvious by the combination of the teachings of the '934 patent and the teachings of Moyer *et al.* Use of the same protein sequence in patentably distinct inventions is not precluded under any statute.

The Examiner reasons that it would have been obvious to one of skill in the art to make the necessary modifications to improve the claimed administration protocol of the '934 patent, thus meeting the limitations of claims 2, 6, 40-42, and 63-64, which are drawn to use of intra-arterial infusion (IA), intramuscular injection (IM), intravenous infusion (IV), and/or subcutaneous injection (SC) to administer FGF in accordance with the administration protocol of the presently claimed invention. Applicant respectfully disagrees. The administration protocol

recited in the presently claimed invention is not taught or suggested by the '934 patent or the Moyer *et al.* reference, nor do the combined teachings of these two cited references provide any motivation for modifying the administration protocols disclosed therein to arrive at this administration protocol. Evidence for this can be found in Moyer *et al.*, where none of the animal models teach or suggest this method of administration. In fact, Yang *et al.* states that "the route of administration may not require local arterial administration", which teaches away from administration to each leg for peripheral artery insufficiency (see page 1435 of Moyer *et al.*).

Further, one could not predict from the results of the clinical trial with CAD using a different administration protocol that the presently claimed method of administration would be beneficial for treating patients with PAD. Only actual experimentation would demonstrate the efficacy of dividing the therapeutically effective amount of FGF into two doses, and administering a single one of these two doses into each leg of a PAD patient within a one hour period. Applicant conceived of this administration protocol for treatment of PAD using FGF and has successfully demonstrated its efficacy in clinical trials.

In view of these remarks, Applicant respectfully submits that use of IA, IM, IV, or SC administration in accordance with the administration protocol of the presently claimed invention is not rendered obvious by these two cited references. Therefore, the limitations of claims 2, 6, 40-42, and 63-64 are not met.

The Examiner also reasons that administration of FGF-2 via the common femoral artery is an art-recognized route of administration for treating intermittent claudication with this therapeutic agent, and thus the limitations of claims 1-82 are met. Applicant respectfully disagrees. As mentioned above, this route of administration is used according to the method of administration recited in these pending claims, and thus the single dose being administered into each leg is administered into the common femoral artery of each leg within a one hour period. Applicant submits that one of skill in the art would not be motivated to administer, via any artery, a dose of FGF into each leg of the patient within a one hour period after reading Moyer *et al.* Therefore, the limitations of claims 1-82 are not met.

As further evidence in support of this obviousness-type double-patenting rejection, the Examiner states that the art recognizes the use of bFGF in the treatment of experimental intermittent claudication and chronic critical leg ischemia via administration of bFGF to femoral arteries, and thus the limitations of claims 7, 8, and 65-73 are met. Applicant respectfully disagrees. For reasons noted above, one of skill in the art apprised of the '934 patent would not be motivated in view of Moyer *et al.* to divide the therapeutically effective dose of FGF into two doses for subsequent administration of a single one of these two doses into each leg of a patient within a one hour period. Thus, the limitations of claims 7, 78, and 65-73 are not met.

Regarding heparin co-administration, Applicant acknowledges that this is a well-known modification in administering pharmaceutical compositions comprising FGF molecules in view of their heparin-binding characteristics. However, recitation of heparin co-administration in a dependent claim does not render obvious the method of administration recited in the respective base claim. In addition, the subject matter in claim 23 is not obvious, as Moyer *et al.* do not teach or suggest the specific method of administration that must be used when the methods of the invention serve as an adjunct to patients undergoing vascular surgery, mechanical bypass surgery, angioplasty, or angiogram. This method of administration is not taught or rendered obvious by these two cited references, either alone or in combination. Therefore, all the limitations of claim 23 and of claims directed to heparin co-administration are not met.

The Examiner also reasons that all the limitations of claims 43-47 drawn to improvements in peak walking time, reduction in body pain, improvement in stair climbing ability, and reduction in the severity of claudication are met because the art recognizes these as clinical endpoints or measures of the clinical effectiveness of a therapy. Applicant submits that these claims, for the reasons mentioned above, are not obvious, and all the limitations of these claims have not been met by the claims of the '934 patent in view of Moyer *et al.*

In summary, the motivation to modify either one of these references, or to combine the teachings of these two cited references, to arrive at Applicant's claimed invention is lacking.

Even if such motivation were to exist, these references do not provide sufficient guidance to one of skill in the art to arrive at Applicant's claimed method of administration. Without this guidance, the combination of the teachings of these two references does not provide to one of skill in the art a reasonable expectation of successfully treating treat PAD, obtaining an improvement in peak walking time in a patient with intermittent claudication, or obtaining an improvement in ankle-brachial index in a patient with intermittent claudication, which are steps that are required in the methods set forth in the amended claims of the present invention. Further, these references fail to teach or suggest all of the limitations set forth in the pending claims. Accordingly, Applicant respectfully submits that a *prima facie* case of obviousness has not been established.

In view of these remarks, Applicant submits that the presently claimed invention and the claims of U.S. Patent No. 6,440,934 are patentably distinct, and are not obvious over the '934 patent in view of Moyer *et al.* Therefore, the obviousness-type double-patenting rejection of claims 1-82 should be withdrawn.

CONCLUSION

In view of the aforementioned remarks, Applicant respectfully submits that the objections to the specification and the rejections of the claims under 35 U.S.C. §112, second paragraph, and under the doctrine of non-statutory obviousness-type double patenting are now overcome. Accordingly, Applicant submits that this application is now in condition for allowance. Early notice to this effect is solicited. If in the opinion of the Examiner a telephone conference would expedite the prosecution of the subject Application, the Examiner is invited to call the undersigned.

It is not believed that extensions of time or fees for net addition of claims are required beyond those that may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR § 1.136(a), and any fee required

therefore (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 16-0605.

Respectfully submitted,

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